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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/871,809	06/04/2001	Batsheva Kerem	24020X	3895

7590 12/09/2003

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EXAMINER
KAM, CHIH MIN

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 12/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/871,809	KEREM, BATSHEVA	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *11/5/03* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

1. Claims 1-8 are pending.

Applicants' response filed September 22, 2003 is acknowledged. Applicants' response has been fully considered, and claims 1-8 are examined.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating cell lines established from samples of cystic fibrosis patient resulting from an abnormal expression of genes caused by aberrant splicing in cells, comprising administering to the cells, an naturally occurring alternative splicing factor (ASF) by transfected the cells with expression vector to produce the ASF, whereby the abnormal expression shifts towards normal expression of the gene, does not reasonably provide enablement for a method of treating individual suffering from a disease resulting from an abnormal expression of genes caused by aberrant splicing in cells, wherein the disease and the abnormal genes are not defined, comprising administering to the cells or to tissue or organs of the individual comprising the cells, an ASF, whereby the abnormal expression shifts towards normal expression of the gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-8 are directed to a method for treating individual suffering from a disease such as cystic fibrosis resulting from an abnormal expression of genes caused by aberrant splicing in cells, comprising administering to the cells or to tissue or organs of the individual comprising the cells, an ASF, whereby the abnormal expression shifts towards normal expression of the gene. The specification, however, only discloses cursory conclusions without data supporting the findings, which states that the method of invention concerns administering to the cells or to tissue or organs of the individual comprising the cells, an alternative splicing factor (ASF), e.g., any factor which is known to modulate alternative splicing, for example, members of the SR protein family including SF2/ASF, the heterogeneous ribonucleoprotein A1 (hnRNP A1), or the agonist of the naturally occurring ASFs, and the administration of the ASFs to the cells causes a shift in the expression of the gene responsible for genetic disease towards normal expression. There are no indicia that the present application enables the full scope in view of a method for treating a disease resulting from an abnormal expression of genes as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the disease treated, the agonists of naturally occurring ASF administered, and the treating conditions of using ASF in various forms, e.g., as a protein product or an expression vector, which are not adequately described or demonstrated in the specification.

(2). The absence of working examples:

There are no working examples indicating the claimed methods in association with the variants except for the examples of several cellular and viral splicing factors that modulate the splicing pattern in epithelial cell line established from the sample of CF patient (Example 5, pages 14-17).

(3). The state of the prior art and relative skill of those in the art:

The related arts, e.g., Mayeda *et al.* (Mol. Cell. Biology 13, 2993-3001 (1993)) teach the essential splicing factor SF2/ASF and hnRNP A1 modulate alternative splicing *in vitro* of pre-mRNAs. An excess of SF2/ASF prevents inappropriate exon skipping in natural β-tropomyosin pre-mRNA, while an excess of hnRNP A1 does not cause inappropriate exon skipping in natural pre-mRNA; Nordqvist *et al.* (Mol. Cell. Biology 14, 437-445 (1994)) teach the adenovirus early region 4 proteins E4 open reading frame (E4-ORF3) and E4-ORF6 regulate major late mRNA accumulation by stimulating constitutive splicing. E4-ORF3 facilitates exon inclusion while E4-ORF6 facilitates exon skipping. However, the related art does not teach the treatment of various diseases resulting from abnormal expression of genes caused by aberrant splicing in cells, and the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on identities of the disease being treated, the

agonists of ASF administered, and the treating conditions for administering ASF as a protein product or an expression vector, to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass a method for treating a disease resulting from an abnormal expression of genes caused by aberrant splicing in cells, comprising administering to the cells an ASF, whereby the abnormal expression shifts towards normal expression of the gene. As indicated in the prior art (Mayeda *et al.*, Mol. Cell. Biology 13, 2993-3001 (1993)), hnRNP A1 can promote alternative exon skipping, however this effect is not universal and is dependent on the size of the internal alternative exon and on the strength of the polypyrimidine tract in the preceding of intron. The specification (e.g., Example 3, Table 2) also indicates transfection of p5T generated two splicing products: 24% of transcripts were aberrantly spliced (330 bp) and the rest (76%) were correctly spliced (513 bp), and transfection of p9T only generated 3% of transcripts being aberrantly spliced; however, transient cotransfection of p5T and pCG-A1 into COS-1 resulted in a substantial increase in aberrantly spliced transcripts (44%) and transient cotransfection of p9T and pCG-A1 does not affect the p9T minigene pattern. Therefore, the invention is highly unpredictable regarding the outcome of the treatment without identifying the abnormal genes in the diseases or the agonists of ASF administered.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method for treating a disease resulting from an abnormal expression of genes caused by aberrant splicing in cells, comprising administering to the cells an ASF, whereby the abnormal expression shifts towards normal expression of the gene. The

specification indicates the effect of overexpression of the cellular hnRNP A1 on the splicing of 3849+10 kb C->T or polyT minigenes, or the effect of overexpression of the viral E4-ORF6 on the splicing of 3849+10 kb C->T minigenes (Examples 2-5; Figs.3-7), where the mutation (3849+10 kb C to T) in the cystic fibrosis transmembrane conductance regulator (CFTR) gene has been linked to CF patients with abnormal epithelial function. However, the specification has not demonstrated the in vivo treatment of a disease, nor has indicated how to extrapolate the in vitro or ex vivo data to in vivo treatment, and there are no working examples indicating the effect of a known ASF in the treatment of the disease. Furthermore, the specification has not indicated the use of any agonist of a naturally occurring ASF, nor has demonstrated the administration of the protein product, ASF to cells is effective in shifting abnormal expression of the gene to normal expression and in the treatment of the disease. Moreover, there are no working examples indicating treating conditions such as effective amount of the ASF protein product for a specific disease in vivo. Since the specification fails to provide sufficient guidance on treating various diseases using a specific AFP or an agonist of the ASF, it is necessary to carry out further experimentation to assess the effects of the ASF in treating the disease due to an abnormal expression of genes caused by aberrant splicing in cells.

(6). Nature of the Invention

The scope of the claims encompass treating a disease resulting from an abnormal expression of genes caused by aberrant splicing in cells, comprising administering to the cells an ASF, whereby the abnormal expression shifts towards normal expression of the gene, but the specification has not demonstrated the disease is treated with an AFP protein or an agonist of

AFP protein in vivo, and the treating conditions for various diseases using the ASF protein product. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the claimed method, the art is unpredictable regarding the outcome of the treatment, and the guidance and the teaching in the specification are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of ASF towards various diseases.

In response, applicants provide four references, which have post filing date, to support the proposition that, to the ordinarily skilled artisan, the in vitro data readily support in vivo treatment, and that the claimed generic inventive subject matter, use of an ASF for treating an aberrant splicing disorder, find broad support in the general knowledge which has developed in the art subsequently to the filing of this application; and applicants also indicate that based on these references, applicant's experimental and prophetic examples have been borne out and the ordinarily skilled artisan would be able to use the claimed method for in vivo treatment of aberrant splicing disorders, and the requirement for additional experimentation indicated by the Examiner is no more than routine experimentation, and the methods of which are well known to those of ordinary skill in the art. Applicants' response has been fully considered, however, the argument is not found persuasive because the references do not teach the use of various ASFs (e.g., SR protein, hnRNP A1, E4-ORF3, E4-ORF6 or an undefined agonist) for the treatment of various genetic diseases, they merely indicate that it is possible to use a specific ASF such as sodium butyrate for the treatment of human SMA patient due to the results of in vitro and in vivo model (Exhibit A), genetic variation in a putative RNA splicing factor influences disease

susceptibility in mice raises the possibility that a similar mechanism modifies the severity of human inherited disorders (Exhibit C), and there is potential to design drugs that target modifier proteins and thus modulate the level of normally spliced transcripts (Exhibit D). Furthermore, sodium butyrate is structurally different from other naturally occurring ASFs, thus, the treating conditions and the effect of this compound is not applicable to other ASFs, and the specification only indicates the in vitro or ex vivo treatment of cells having abnormal expression of genes caused by aberrant splicing, and administration of an ASF to the cells shifts the abnormal expression towards normal expression of the gene, however, this shift is not universal (see the section of Predictability or unpredictability of the art; Fig. 4 and Table 2), thus, the outcome of the treatment is unpredictable. Moreover, the art and the specification do not teach the use of various ASFs in the treatment of the disease in vivo, and there is no teaching on how to extrapolate the in vitro data to in vivo treatment. Therefore, the full scope of the claims is not enabled.

3. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-8 are directed to a method for treating individual suffering from a disease (e.g., cystic fibrosis) resulting from an abnormal expression of genes caused by aberrant splicing in cells, comprising administering to the cells or to tissue or organs of the individual comprising the cells, an alternative splicing factor (ASF), whereby the abnormal expression shifts towards normal expression of the gene. The specification indicates that ASF may be administered to the

cells by inserting a nucleotide sequence expressing the ASF in an expression vector, and the cells of the individual are transfected with the expression vector to produce ASF, or by attaching the expression vector to targeting moiety, e.g., antibody or a ligand of a specific receptor which can specifically bind to the membranes of the desired cells, and the expression vector being administered systemically, or by administering ASF as the protein product itself (page 5, line 26-page 6, line 25). However, the specification only indicates the in vitro or ex vivo effect of administering AFP to the cell lines, e.g., the effect of overexpression of the cellular hnRNP A1 on the splicing of 3849+10 kb C->T or polyT minigenes, or the effect of overexpression of the viral E4-ORF6 on the splicing of 3849+10 kb C->T minigenes (Examples 2-5; Figs.3-7), it has not demonstrated the in vivo treatment of various diseases resulting from an abnormal expression of genes caused by aberrant splicing in cells, e.g., the administration of a ASF protein to cells is effective in shifting abnormal expression of the gene to normal expression and in treating the disease. Furthermore, there are no in vivo working examples indicating the treating conditions such as effective amount of the ASF for a specific disease, and the effect of the ASF in aberrant splicing of the genes and in the treatment of disease. Without guidance on the treating conditions of ASF on the disease, one skilled in the art would not know how to use the ASF. The lack of description in the treatment of the disease using the ASF as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-8 are indefinite because the claims lack essential steps in the method of treating an individual suffering from a disease resulting from an abnormal expression of genes caused by aberrant splicing. The omitted step is the outcome of the treatment, it is not clear what effect the administration of ASF would produce in the treatment of disease. The term "treating said disease" does not indicate the outcome of the treatment. Claims 2-8 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

5. Claims 3 and 4 are indefinite because the claim recites a mutation of "3849+10kB C->T" or "5T allele", but the claim does not identify the gene having the mutation, therefore it is not clear which gene has the mutation.

Conclusion

6. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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December 4, 2003

Christopher S. F. Low
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SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600